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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,148	03/01/2004	Amedeo Leonardi	04266/100M619-US3	3142

7278 7590 09/30/2005

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,148	LEONARDI ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 15, 2005, has been considered.

Prior Office Action

The office action mailed July 29, 2005 is vacated in favor of the following:

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaviraghi et al., US 6,071,939 ('939), Sada et al.,US 6,878,703 B2 in view of New drug evaluation, No. 20, April 1998, Gasser et al., 1999 J. Clinical and Basic Cardiology (2) 169-174 and Norwood et al., Drug forecast, Olmesartan Medoxomil for hypertension: A clinical review.

Gaviraghi et al., teach in regard to current claim(s) 1, 8, 11, 4, 5, 9, 10,14, 15, 21, 29, 30, 32, 40, 43, 50, and 56 a method of treating hypertension (current claim 1) administering an angiotensin II receptor (current claims1, 8, 11 and 13)(column 1 line 19-20) antagonist (telmisartan column 1 line 19) and a calcuim channel blocker (current claim 1) lacidipine (column 1 line 14). The patent '939 teaches combination of lacidipine and telmisartan provided an unexpectedly advantageous combination for the treatment of hypertension column 1 lines 30+. Gaviraghi et al., also teach the dosage range of the angiotesin II receptor blocker (current claims 4, 9, 14, 15, 21, 29, 32, 40, 43, 50 and 56) to be 10mg- 100mg and the calcium channel blocker to be 1-6mg at column 3 lines 39+, see current claim 9 (i) as disclosed by applicant, and is taught at column 3 lines 40+ of the patent, and 20 mg of second amount (current claims 10,15, 22, and 30) at column 5, line 47+, where 0.2 mg/kg of the second drug and 1mg/kg angiotesin II receptor was administered. Upon calculation, based on the average weight of a human being of 70 kg, about 14 mg of the second drug, would have been administered. Where the individual weighs more, e.g., 100 kg, the equivalent amount of

angiotesin II receptor is 20 mg, making the claim limitation obvious because the amount of angiotesin II receptor administered is the same. At 150 kg the equivalent is 150 mg, of angiotesin II receptor would have been administered.

Gaviraghi et al., also teaches the limitation(s) of current claims 57-66, a controlled release formulation of the drug lacidipine and telmisarta.

While, Gaviraghi et al., did not teach administering the diuretic of claims 2, 6-7, 67-71. Sada et al., teach in regard to current claim(s) 1, 2, 6-7, 27, 67-71 administering an angiotensin II receptor antagonist (claim 1) and a diurectic (claims 2, 6-7, 27, 67-71) for the treatment of hypertension column 1 lines 13+, where the diuretic is a chlorthalidione (claims 6, 7,18, 27, 36, 37, 70-71) (column 4 line 54) or a hydrochlorothiazide (column 4 line 58)(claims 6,7,36,37, 68-69).

The New Drug evaluation reference teaches in regards to claim(s) 10, 15,17, 24, 31 lercanidipine administered to mild –moderate hypertension patients at 10 mg or 20 mg daily (see page 1 of reference). Mild to moderate represents patients whose high blood pressure was lowered with treatment.

Gasser et al., teach in regard to current claim(s) 30, 48-49, 54-55 administering lercanidipine as low as 5 mg/day (page 171 therapeutic use) to 40mg/day. Gasser, also teach as in current claims 16 and 23 a patient population of non-responders at page 171.

The Drug forecast reference teaches current claim(s) 3, 8, 12, 13, 19, 20, 25-26, 28, 38, 39, 42 45-47 administering olmesartan medoxomil as in claim 3 and 13, for treatment of hypertension at dosages ranging from 2.5-80 mg as shown on page 614

(clinical efficacy) and table 2 of the same page. Drug forecast also teach irbesartan, as in claim 20, telmisartan (same drug taught by Gaviraghi) are also angiotensin II receptor blockers and the dosage on page 614 table 2 and also of irbesartan (claim 8, 51-53) on the same page. The reference also teach hydrochlorothizide administered from 25-50mg/day page 614 second column-Puchler study lines 4+ as in claims 19, 25-26, 28, 38. The reference also teach (see table 2 list of drugs and dosage amounts given) irbesartan current claims 33, 42, 44 the amount from about 150-300, also teach moderate top severe hypertensive patients thus includes tachycardia patients (see puhcler study-below table 2) as in claims 34-35, 41.

The claims differ where Gaviraghi administers telmisartan and lacidipine to treat hypertension instead of a olmesartan and lercanidipine combination.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to replace the drug telmisartan and lacidipine as taught by Gaviraghi with that of olmesartan and lercanidipine as disclosed by Gasser and the New Drug reference to provide for the treatment of hypertension as in current claims 1-71. Combination drug therapy would vary, per individual basis, some patient respond to one set of drug will vary from another i.e., (tolerance), therefore the varying combinations of drugs are needed to treat the same condition, e.g., telmisartan and lacidipine with a diurectic or olmesartan and lercanidipine with a diurectic (same effect) are expected to give options to treatment of individuals in need thereof.

One of ordinary skill in the art would have known that using olmesartan and lercanidipine combination in place of lacidipine and telmisartan would work because

each are well known drugs used for the treatment of hypertension. Telmisartan and olmesartan medoxomil are well known angiotensin II receptor drugs having the same function in the treatment of hypertension. Lacidipine and lercanidipine are functionally equivalent and are both calcium channel blockers used in the treatment of hypertension. Gaviraghi also teaches that combining or co-administration of telmisartan and lacidipine, has a synergistic, antihypertensive effect, andimprovement of blood pressure control was achieved (see column 1 lines 35+).

Gaviraghi et al., teach that telmisartan and lacidipine was used to treating hypertension, in patients to show the combinatory effect of the drug administered. The result showed significant reduction effect in the mean blood pressure and the heart rate (column 5 line 45-67), i.e., motivation to and for one of ordinary skill in the art to practice. Although, this study did not per se teach the combination as disclosed by applicant, it teaches the use of an angiotensin II receptor blocker combine with a calcium channel blocker and that affects hypertension. Gaviraghi et al.,also teach a formulation for controlled release, thus making it obvious to one of ordinary skill in the art to formulate a drug as claimed by applicant to be released slowly upon administration.

Sada et el teach in addition to the angiotensin II receptor blocker as a diuretic (current claim 2) to be hydrochlorothiazide (current claim 6). It is known that co-administration of an angiotensin and a diuretic is an effective therapy for treatment of hypertension (column 1 lines 28+). Sada also teaches the effect of co-administration of the drugs result in switching on signals at their respective receptors to cause

pharmacological actions (column 11 lines 47+),resulting in decreases in plasma concentration below the threshold plasma levels.

One of ordinary skill in the art would have expected successful results in administering an angiotensin II receptor blocker together with a calcium channel blocker and a diuretic to treat hypertensive patients since both are successful separately. Therefore, one of ordinary skill would have been successful combining the teaching of the selection of olmesartan medoxomil and lercanidipine for the treatment of hypertension and using a diuretic. Diurectics have been used to treat hypertension patients. One of ordinary skill in the art would have combined the teaching of Gaviraghi with that of Sada, to lower the heart rate of the hypertensive individual or patient and thereby ameliorate hypertension. Both references teach combining an angiotesin II receptor with a calcuim channel blocker or using an agiotensin II receptor with a diurectic gave better result in lowering the blood pressure.

Further, one of skill would have been motivated to combine the teachings of Gaviraghi with that of Sada, New Drug, Gasser and Norwood as disclosed by administering the doses (in claims 4 etc) and expect a successful result in the treatment of hypertension. Using drug doses taught by Drug forecast (administering olmesartan medoxomil for hypertension at dosages ranging from 2.5-80 mg as shown on page 614) together with 25-50mg/day of the diurectic and lercanidipidine from 5mg –40 mg as taught by Gasser, one skilled in the art would expect to treat various population of hypertensive patients with different combinations of olmesartan medoxomil/ lercanidipine and hydrochlorothizide.

Claims 4, 9, 14, 21, 29, 32, 40, 43, 50 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaviraghi et al., US 6,071,939, Sada et al.,US 6,878,703 B2 in view of New drug evaluation, No. 20, April 1998, Gasser et al., 1999 J. Clinical and Basic Cardiology (2) 169-174 and Norwood et al., Drug forecast, Olmesartan Medoxomil for hypertension: A clinical review as applied to claims 1-7 and 67-71 above, and further in view of Physicians Desk Reference (PDR) (C) Sanko Pharm Inc 2002.

While the combined references of Gaviraghi et al., Sada et al., New drug evaluation, No. 20, Gasser et al., Norwood et al., do not teach claims 4, 9, 14, 21, 29, 32, 40, 43, 50 and 56 wherein there are variation of administration of the first amount (an agiotensin II receptor blocker) and the second amount (calcium channel blocker), as olmesartan and lercanidipine.

The PDR teaches (see highlighted section) olmesartan medoximil on page 3 of reference (general) is administered up to 320 mg or given in multiple doses of up to 80 mg, (Claims 5) the reference also teach on page 5 angiotensin receptor blockers and hydrochlorthiazide had the effect of lowering blood pressure.

Gaviraghi et al., also teach of the dosage range of the angiotesin II receptor blocker (claims 4, 9, 14, 21, 29, 32, 40, 43, 50 and 56) to be 10mg- 100mg and the calcium channel blocker to be 1-6 mg at column 3 lines 39+, see claim 9 (i) as disclosed by applicant, and is taught at column 3 lines 40+ of the patent.

Since the PDR teaches the dosage range of olmesartan medoximil, one of ordinary skill in the art would have combined the teachings of Gaviraghi with that of

Sada, New Drug, Gasser and Norwood with that of PDR, and expect a successful result in varying or optimizing the doses, form mild to high hypertensive patients. Gaviraghi already teaches of the combinatory effect of telmisartan and lacidipine (see column 3 lines 39+) and column 2 lines 59 + where the patent teaches that the combination amount will vary according to the body weight, age, general condition and severity of the disease. One skill in the art would know that any combination of an angiotensin II receptor with a calcium channel blocker would be successful, as several variation of the combination already exist (see above discussion). With regards to the different population treated, as taught by Gaviraghi, column 2 line 59+ depending on the severity of the hypertension (for example –tachycardia where the heart rate is very high) the dosage is optimize or determined by one of ordinary skill in the art. One of ordinary skill in the art would have been motivated to use olmesartan medoximil/irbesartan and lercanidipine instead of telmisartan and lacidipine since olmesartan medoximil/irbesartan and lercanidipine is also taught by the above references.

Further, one of skill would have been motivated to combine the teachings of Gaviraghi, Sada, New Drug, Gasser and Norwood with that of PDR because the drugs in question are functionally similar to the drugs used by the above reference;

a) angiotensin II receptor blocker

b) calcium channel blocker

Thus the claimed invention was prima facia obvious to make or use at the time it was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SVS
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9/12/05

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